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10/789,400	02/27/2004	Peter L. Collins	4239-67784-01	5376

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	
MAIL DATE	**DELIVERY MODE**
09/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,400	COLLINS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *9-14, 20-24, 27-54, 57, 60 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,15-19,25,26,55,56,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment and Dr. Peter Collins's declaration filed 7-9-07 have been entered. Claims 1, 6, 17, 25 and 55 have been amended. Claims 58-61 have been added. The newly added claims 60 and 61 depend from non-elected claims 20 and 21, respectively, therefore, claims 60 and 61 will NOT be considered by Examiner. Claims 1-61 are pending. Claims 1-8, 15-19, 25, 26, 55, 56, 58 and 59, and rHMPV comprising one or more attenuating nucleotide modification or comprising one or more nucleotide substitution that reduces or ablates expression of rHMPV M2-2 ORF, are under consideration.

This application contains claims 9-14, 20-24, 27-54, 57 and newly added claims 60 and 61 are drawn to an invention nonelected with traverse in the reply filed on 11-27-06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Double Patenting

1. Claim 8 remains objected to under 37 CFR 1.75 as being a substantial duplicate of claim 18. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Only rHMPV M2-2 ORF is considered in claim 8, therefore, claims 8 and 18 are duplicate claims.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 7-9-07 necessitates this new ground of rejection.

The phrase "wherein the phenotypic change comprises at least one change selected from a change in growth properties in cell culture ..., and a change in immunogenicity" in claim 25 remains vague and renders the claim indefinite. It is unclear whether the "at least one change" is selected from the following list of change with or without "a change in immunogenicity". It is unclear whether "a change in immunogenicity" has to be included in the "at least one change" or not regardless which change is selected. Changing the phrase to "wherein the phenotypic change comprises at least one change **selected from the group consisting of** a change ..., and a change in immunogenicity" would be remedial. Claim 26 depends from claim 25.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-8, 15-19, 25, 26, 55 and 56 remain rejected and newly added claims 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written

description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is repeated for the reasons set forth in the preceding Official action mailed 1-9-07. Applicant's arguments filed 7-9-07 have been fully considered but they are not persuasive.

Applicants argue that the claimed invention relates to a finding that ablation of expression of particular genes of HMPV produces a controllable level of attenuation in creating vaccine strains. The generic invention relates to these modifications and their use among various HMPVs, not to the other variation in HMPV itself. Applicants further argue that Examiner's reasoning about potential variation in protein structure is irrelevant to the present claims since the protein in question is not expressed (amendment, p. 13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-07. The claims read on any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein that are derived from any virus or any source. The claims encompass a genus of various rHMPV strains and substrains having different nucleotide sequences. The specification only discloses the nucleotide sequence of HMPV strain 83 (SEQ ID No. 1) and HMPV strain 75 (SEQ ID No. 2). Since HMPV was described only recently (see specification, p. 1, last paragraph) and the specification only discloses the sequences of HMPV strain 83, strain 75 and strain 001, it is apparent that applicants do NOT have possession of the nucleotide sequences of

the unknown and unidentified HMPV strains encompassed in the claims. Further, the claims encompass one or more attenuating nucleotide modification comprising a **partial** or complete deletion of M2-2 ORF or one or more nucleotide substitution that **reduces** or ablates expression of the M2-2 ORF. It is not necessary to ablate expression of M2-2 ORF. Partial deletion of M2-2 ORF or one or more nucleotide substitution may only change the encoded M2-2 protein sequence rather than ablate its expression. The modified nucleotide sequence of M2-2 ORF of any HMPV could differ dramatically from the disclosed M2-2 ORF sequence, and said modified nucleotide sequence could encode dramatically different amino acid sequences or not encode any amino acid sequence at all. The claims encompass various modified nucleotide sequences encoding a genus of numerous structural variants of the amino acid sequence encoded by the disclosed M2-2 ORF. The specification fails to provide the structural features of the variant proteins and the biological function of the variant proteins was unpredictable at the time of the invention (discussed below). The specification also fails to provide guidance for whether those variant proteins could result in the phenotypic change as recited in the claims. Therefore, the potential variation in protein structure is relevant to the claimed invention. Even if the expression of M2-2 ORF has been ablated, the resulting phenotype of the rHMPV was still unpredictable at the time of the invention. Thus, the limited information disclosed is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed recombinant HMPVs and expression vector comprising said HMPVs.

Applicants argue that Figures 7-25 show that the applicants were in possession of the invention as claimed (amendment, p. 14, 1st paragraph). This is not found persuasive because of

the reasons set forth in the preceding Official action mailed 1-9-07 and the reasons set forth above. Figures 7-25 only shows the use of rHMPV83.

6. Claims 1-8, 15-19, 25, 26, 55 and 56 remain rejected and newly added claims 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the recombinant HMPV lacking M2-2 ORF as disclosed in the specification, does not reasonably provide enablement for any recombinant human metapneumovirus (rHMPV) comprising a partial or complete recombinant HMPV genome or antigenome comprising one or more attenuating nucleotide modification comprising a partial or complete deletion of M2-2 ORF or one or more nucleotide substitution that reduces or ablates expression of the M2-2 ORF, and a N protein, a P protein and a L protein that are derived from any virus or any source, wherein said rHMPV results in the phenotypic change recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 1-9-07. Applicant's arguments filed 7-9-07 have been fully considered but they are not persuasive.

Applicants reiterate the argument regarding lack of written description and argue that Examiner's arguments are totally irrelevant to the claimed invention since the claimed invention relates to ablation of expression of a protein. Applicants further argue that Examiner only consider unpredictability, therefore, the lack of enablement is therefore legally insufficient (amendment, p. 14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-07 and the reasons set forth above. Examiner discussed the

nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art. The unpredictable nature of the art requires one skilled in the art at the time of the invention undue experimentation to practice over the full scope of the invention claimed.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-4, 6-8, 15, 16, 18, 25, 55 and 56 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bermingham et al., 1999 (PNAS, Vol. 96, pp. 11259-11264, IDS) in view of van den Hoogen et al., 2001 (Nature Medicine, Vol. 7, No. 6, p. 719-724, IDS) and van den Hoogen et al., 2002 (Virology, Vol. 295, p. 119-132, IDS) and is repeated for the reasons set

forth in the preceding Official action mailed 1-9-07. Applicant's arguments filed 7-9-07 have been fully considered but they are not persuasive.

It is noted that the declaration by Dr. Peter Collins has not been signed, therefore, the declaration will NOT be considered.

Applicants cite Dr. Peter Collins's declaration and argue that the art of recombinant virus production is among biotechnology arts, which is considered "inherently unpredictable". It is unpredictable whether the life cycle of a first virus would be mimicked by the life cycle of a different virus, and there is no reasonable expectation of success that the present invention can be obtained by the same genome modification as that in RSV (amendment, p. 15). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-07. As discussed above, the declaration by Dr. Peter Collins has not been signed, therefore, the declaration will NOT be considered. Thus, the arguments regarding Dr. Collins's declaration renders moot. It is not necessary that all fields in biotechnology arts are inherently unpredictable. Some field, such as gene therapy in vivo, is unpredictable, however, some field, such as recombinant protein production in vitro, is not unpredictable. It would have been obvious for one of ordinary skill in the art at the time of the invention to construct a recombinant HMPV or an expression vector having a partial or complete HMPV genome or antigenome comprising one or more attenuating nucleotide modification as claimed because Bermingham teaches construction of such recombinant human RSV and van den Hoogen teaches the nucleotide sequence of HMPV, and both human RSV and HMPV are members of Pneumovirinae subfamily and clinical symptoms for human RSV and HMPV are largely similar. There is no evidence of record that shows unpredictability in using the method taught by

Bermingham to construct the recombinant HMPV as claimed. It is noted that the claims are product claims that read on recombinant HMPV and the intended use f the product does not carry weight in the 35 U.S.C. 103(a) rejection. Since the nucleotide sequence of HMPV was disclosed by van den Hoogen, there is reasonable expectation of success in preparing the claimed recombinant HMPV in view of the teachings of Bermingham, and van den Hoogen.

10. Claims 1 and 3-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bermingham et al., 1999 (PNAS, Vol. 96, pp. 11259-11264, IDS) in view of van den Hoogen et al., 2001 (Nature Medicine, Vol. 7, No. 6, p. 719-724, IDS) and van den Hoogen et al., 2002 (Virology, Vol. 295, p. 119-132, IDS) as applied to claims 1-4, 6-8, 15, 16, 18, 25, 55 and 56 above, and further in view of Ludin et al., 1996 (Gene, Vol. 173, p. 107-111) and is repeated for the reasons set forth in the preceding Official action mailed 1-9-07. Applicant's arguments filed 7-9-07 have been fully considered but they are not persuasive.

Applicants argue that the combination of Bermingham and van den Hoogen does not establish prima facie obviousness of the invention as argued before, and Ludin does nothing to remedy the deficiencies of the combination of Bermingham with van den Hoogen (amendment, p. 15-16). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 1-9-07 and the reasons set forth above.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER